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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/171,081	12/14/1998	SASA KRANJC	22681-0002	7627

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EXAMINER

PRATS, FRANCISCO CHANDLER

ART UNIT	PAPER NUMBER
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1651

DATE MAILED: 02/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/171,081	Applicant(s) KRANJC ET AL.	
	Examiner Francisco C Prats	Art Unit 1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 January 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 36-38 and 41-55 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 36-38 and 41-55 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 22, 2004, has been entered.

Claims 36-38 and 41-55 are pending and are examined on the merits.

Claim Rejections - 35 USC § 102

Claims 36-38, 42-45, 47, 49, 51 and 52 are rejected under 35 U.S.C. 102(b) as being anticipated by Cole et al (U.S. Pat. 4,110,165).

Cole discloses processes of making clavulanic acid wherein the claimed microorganism, *Streptomyces clavuligerus*, is cultivated in a fermentation medium. Note specifically the potassium dihydrogen phosphate concentration of 0.1% in the fermentation disclosed in Example 13 at column 23. Note further that about 55% of the dipotassium hydrogen phosphate in the fermentation medium in Example 9, at column 21, is "assimilable"

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phosphorus, i.e. phosphate, and that therefore the medium in Example 9 contains about 1.10 grams of assimilable phosphorus per liter of medium which is about 0.11% assimilable phosphorus, well within the claimed range concentration. Therefore, in at least Examples 9 and 13, the starting phosphorus concentration is below the claimed amount. Moreover, no phosphorus is added during the fermentation, and the fermentations last for 3-5 days. Thus, the processes disclosed in Examples 9 and 13 necessarily meet the limitation requiring the microorganism to be grown within the claimed phosphorus concentration range, and also meet the limitation requiring a decrease in the phosphorus concentration. Moreover Example 9 uses "Arkasoy," or soy flour as the nitrogen source. See column 20, lines 1 and 2. A holding of anticipation over the cited claims is therefore required.

Claim Rejections - 35 USC § 103

Claims 36-38, 41-47 and 49-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cole et al (U.S. Pat. 4,110,165).

As discussed above, Cole is considered to anticipate claims 36-38, 42-45, 47, 49, 51 and 52, because Cole discloses processes of making clavulanic acid wherein the claimed

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microorganism, *Streptomyces clavuligerus*, is cultivated in a fermentation medium containing the claimed amounts of nutrients, including phosphate.

Cole differs from the claims in that Cole does not explicitly disclose processes wherein the phosphorus concentration is about 0.008%, as recited in claim 41. However, Cole discloses the desirability of phosphate in the fermentation media used therein. Moreover, nutrient concentrations in fermentation media are result-effective parameters whose values are determined through routine experimentation by artisans of ordinary skill. Therefore, the determination of suitable phosphate concentrations, such as recited in claim 41, must be considered *prima facie* obvious absent some demonstration of an unexpected result coming from the use of that concentration. The range of carbon source concentrations recited in claim 50 must also be considered obvious for similar reasons, particularly in view of Coles's explicit disclosure of carbon source concentrations encompassing a significant portion of the values recited in applicant's claims. See column 10, lines 39-42.

Also, the use of sodium dihydrogen phosphate as the phosphorus source, recited in claim 46, must be considered obvious over Cole's disclosed use of potassium dihydrogen

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phosphate as the phosphorus source, the artisan of ordinary skill reasonably expecting the salts of potassium and sodium to function substantially equivalently in the processes disclosed by Cole, especially in view of Cole's disclosure that either of the salts of phosphoric acid may be used. See column 10, lines 56-57. Lastly, the use of large volume fermentations in the processes disclosed by Cole, recited in claims 53 and 54, must be considered obvious, in view of the fact that it would have been economically desirable to have produced larger quantities of the desired compound. A holding of obviousness over the cited claims is required.

Claims 36-38 and 41-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cole et al (U.S. Pat. 4,110,165) in view of Stanbury et al (*Principles of Fermentation Technology*, Pergamon Press, New York, 1984, pages 11-25).

As discussed above, Cole is considered to anticipate claims 36-38, 42-45, 47, 49, 51 and 52, and to render obvious claims 36-38, 41-47 and 49-54. Cole does not explicitly disclose conducting the fermentations as fed-batch or continuous processes, as recited in claims 48 and 55. However, Cole clearly discloses that 0.1% is a suitable concentration of phosphorus for fermentative production of clavulanic acid. See

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Example 13. Thus, the artisan of ordinary skill at the time of applicant's invention clearly would have been motivated by Cole's disclosure of the suitability of 0.1% phosphorus to have ensured the presence of that amount of phosphorus, in continuous or fed-batch processes of the type disclosed by Stanbury. Additional motivation for using the fed-batch systems disclosed by Stanbury would have been derived from the fact that clavulanic acid is a very similar molecule to penicillin, and Stanbury discloses that fed-batch processes are particularly desirable in fermentations which produce antibiotics such as penicillin. See Stanbury at 23, discussing the applicability of fed-batch fermentation to penicillin production. A holding of obviousness over the cited claims is therefore required.

Claims 36-38 and 41-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cole et al (U.S. Pat. 4,110,165) in view of Stanbury et al (*Principles of Fermentation Technology*, Pergamon Press, New York, 1984, pages 11-25), as applied above to claims 36-38 and 41-55, and in further view of Puentes et al (EP 0 182 522 A1).

As discussed above, Cole obviates claims 36-38 and 41-55 when taken in view of Stanbury. With the exception of *Streptomyces clavuligerus*, neither of those references discloses

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the production of clavulanic acid from all of the microorganisms recited in claim 47. However, Puentes et al disclose that all of the claimed microorganisms were known at the time of applicant's invention to produce clavulanic acid in known media containing carbon sources, nitrogen sources and inorganic salts. See page 2. Thus, the substitution of any known clavulanic acid-producing species for that disclosed in Cole clearly would have been considered an obvious matter of selecting from known equivalents, the artisan of ordinary skill reasonably expecting from Puentes that the microorganisms disclosed therein would be able to produce clavulanic acid in the fermentation media disclosed by Cole. Thus, absent some unexpected result inhering from the use of the claimed microorganisms, the claims must be considered obvious in this respect.


No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Francisco C Prats whose telephone number is 571-272-0921. The examiner can normally be reached on Monday through Friday, with alternate Fridays off.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


Francisco C Prats
Primary Examiner
Art Unit 1651

FCP